methods of using these polynucleotides for HLA-DR typing."

The Examiner also contends that:

> "[s]ince the specification has only described three specific DR-beta sequences and because the genus of the sequences encompassed by the recitation in the claims is enormous with no common structural feature, the three species described in the specification are not representative of the genus."

More particularly, the Examiner asserts that:

> " . . . the claims are drawn to a method using DNA sequences which are capable of hybridizing to polymorphic sequences which makes the genus of DNA sequences which can be used in the method even larger. Sequences identified by hybridization would not predictably have the same structural and functional characteristics as the disclosed species because there is no way to determine what variations would be tolerated without making the method inoperable as a typing method."

The Examiner's contentions are without merit, particularly when viewed in light of the Declaration of Dr. Jack L. Strominger, a pioneer in the field of HLA antigens, filed concurrently herewith.

Testifying as to the skill of the art at applicants' effective filing date, Dr. Strominger states that:

> "the '786 application identifies and characterizes three specific polymorphic regions (i.e., amino acids 8-14, 26-32 and 72-78) and one specific conserved region (i.e., amino acids 39-45) and DNA sequences encoding those regions from three specific HLA-DR-β chain alleles (i.e., HLA-DR-β-A, HLA-DR-β-B and HLA-DR-β-C). Based on that teaching, it is my opinion that a person of skill

> in the art as of July 30, 1982, would appreciate common features for identifying HLA-DR-β chain alleles, other than HLA-DR-β-A, HLA-DR-β-B and HLA-DR-β-C alleles, and DNA sequences capable of hybridizing to a polymorphic region selected from amino acids 8-14, 26-32 or 72-78 of such other HLA-DR-β chain alleles." (Strominger Decl. ¶ 12).

Dr. Strominger goes on to state that a person of skill in the art as of the July 30, 1982 filing date would have understood the utility of the present invention, and known how to exploit the three polymorphic regions and one conserved region, taught in the instant application, for HLA-DR typing.

Additionally, Dr. Strominger explains that, as a person of skill in the art as of July 30, 1982, it would have been possible for him to use the conserved and polymorphic DNA sequences of the '786 application to identify other HLA-DR-β alleles. (Strominger Decl. ¶ 17). In essence, Dr. Strominger believes that applicants' identification of amino acid regions 8-14, 26-32 or 72-78 of HLA-DR-β-A, -B, and -C as "polymorphic regions" of HLA-DR-β, provided a common structural feature, which, when combined with applicants' identification of amino acid regions 39-45 of HLA-DR-β-A, -B, and -C as "conserved regions" of HLA-DR-β, provided structural features characteristic of, and allowing identification of, additional HLA-DR-β alleles, in turn allowing identification of DNA sequences capable of

hybridizing to those polymorphic regions of those additional HLA-DR-β alleles, for use in HLA-typing. (Strominger Decl. ¶¶ 13-14).

Furthermore, Dr. Strominger cites Exhibit K as confirmation of the usefulness of applicants' polymorphic and conserved regions of HLA-DR-β. (Strominger Decl. ¶¶ 18-21). Dr. Strominger explains, that all HLA-DR-β genes share the structural similarity of the "conserved region" first identified by applicants at amino acids of 39-45 of HLA-DR-β and the three "polymorphic regions" first identified by applicants at amino acids 8-14, 26-32 and 72-78 of HLA-DR-β. Dr. Strominger goes on to state that there is sufficient "structural detail" provided by applicants' disclosure to allow one of skill in the art as of July 30, 1982 to identify additional HLA-DR-β alleles. In fact, Exhibit K of Dr. Strominger's Declaration confirms that among the HLA-DR-β alleles identified, sequenced and aligned as of January 2002, among the 363 sequenced and aligned HLA-DR-B1, HLA-DR-B3, HLA-DR-B4, and HLA-DR-B5 alleles, all but 14 alleles have 100% homology at the region of amino acids 39-45, which was first identified in the present application as a conserved region. Additionally, of the 14 inexact matches, 6 of the alleles differ

only by a single amino acid substitution, and the remaining 8 alleles are all HLA-DR-B4 alleles.

Dr. Strominger's expert testimony confirms that applicants' disclosure of a single conserved region of HLA-DR-β and three polymorphic regions of HLA-DR-β provided a predictability of structure which reasonably conveyed to one of skill in the art at the time that the inventors were in possession of the claimed invention. Such disclosure satisfies the written description requirement:

> "predictability of the structure of a species can be premised on (1) whether the level of skill in the art leads to a predictability of structure; and/or (2) whether teachings in the application or prior art lead to a predictability of structure." The Written Description Guidelines, Section II.A.

The official comments to the Written Description Guidelines emphasize that "describing the complete chemical structure, i.e., the DNA sequence, of a claimed DNA is one method of satisfying the written description requirement, but it is not the only method", and "there is no basis for a per se rule requiring disclosure of complete DNA sequences or limiting DNA claims to only the sequences disclosed." 66 Fed. Reg. at 1101. Rather, another way of fulfilling the written description requirement is by disclosing sufficiently detailed, relevant identifying characteristics to provide evidence that applicants

were in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed function and structure, or some combination of such characteristics. 66 Fed. Reg. at 1101. Assessed by this test, it is clear that applicants' specification provides written description for the subject matter claimed herein.

The HLA-DR typing methods and kits of this invention are characterized by DNA sequences which are capable of hybridizing to a polymorphic region of HLA-DR-β chain locus to allow the determination of one or more HLA alleles, for use in rapid and accurate HLA-DR typing of individuals. Because the structures of the claimed polymorphic regions are defined in the instant application, the structure of the complementary sequences, i.e. sequences which hybridize to said polymorphic regions, are also defined by the instant application. Furthermore, the fact that the DNA sequences which characterize applicants' HLA-DR typing methods and kits are required to hybridize to one of the defined polymorphic regions of an HLA-DR-β chain locus and allow the determination of one or more HLA alleles provides the requisite functional and structural characteristics to adequately describe them.

With respect to claims 78-79, the Examiner contends that:

> "[t]he claims are not limited to the DNA sequences consisting of the specifically described regions of amino acids 8-14, 26-32, 39-45 or 72-78 of HLA-DR-beta -A, -B, -C... The DNA sequence is not even limited to coding for the same amino acids as in the described regions because the claims recite that [the] DNA encodes a majority of the amino acid sequence in the region of amino acids ... of nucleic acid X."

Claims 78 and 79 have been amended to include the language suggested by the Examiner, with respect to the use of the phrase "majority".

With respect to the Examiner's reliance on Vas-Cath, applicants note that the identification of the amino acid regions of 8-14, 26-32, or 72-78 of HLA-DR-β as "polymorphic", and the identification of the amino acid region of 39-45 as "conservative", served as the common structural features that led to the identification of over 300 additional HLA-DR-β alleles. In fact, without applicants' description of these conserved and polymorphic regions, the skilled artisan would have had no idea which regions of HLA-DR were important, and necessary, to carry out HLA-DR typing. Applicants' identification of the exact regions of polymorphism and single conserved region within HLA-DR, provided the necessary "description" required to carry out the claimed methods and processes of HLA-DR typing.

With respect to the Examiner's assertion that the amended claims are not limited to the embodiments described in the specification because "any DNA can hybridize to any other DNA molecule under low stringency hybridization", applicants refer to paragraphs 24 to 31 of Dr. Strominger's Declaration in rebuttal. Dr. Strominger agrees "whole-heartedly" with Dr. Lathe's description of the state of the art of hybridization-based molecular biology as of July 30, 1982, explaining that:

> "the concepts of DNA hybridization were well understood" and agrees with Dr. Lathe's statement that "hybridization assays were of such routine nature in molecular biology labs . . . such assays would not involve undue experimentation." See Exhibit F of Lathe Declaration. (Strominger Decl. ¶¶ 24-26).

Additionally, in paragraph 29 of his declaration, Dr. Strominger explains that "the person of skill in the art as of July 30, 1982 would have know that the hybridization techniques of the '786 application would not be carried out under low stringency hybridization conditions." Finally, Dr. Strominger states that:

> "Because the person of skill in the art as of July 30, 1982 would have understood the basic concepts of DNA hybridization, and how to employ hybridization techniques in conjunction with HLA-DR typing methods, it is my opinion that the claim recitation: "DNA sequences hybridize to specifically defined polymorphic regions of an HLA-DR-beta chain locus" would be fully understood by the person of skill in the art as of July 30, 1982. As such I believe the Examiner's assertion on this point to be without scientific merit." (Strominger Decl. ¶ 30)

It is clear from the expert testimony of both Drs. Lathe and Strominger, that a person skilled in the art at July 30, 1982 would have know that the use of low temperatures for hybridization would have merely frustrated any attempts to identify DNA sequences, which specifically hybridize. Accordingly, those temperatures would not have been employed.

As to the Examiner's concern that the full-length DR-A, DR-B and DR-C sequences would not be useful for HLA-typing, Dr. Strominger states that the mere teaching of short, synthetic probes, based on the polymorphic and conserved regions taught by applicants, does not in anyway diminish the utility of the full length cDNA inserts for HLA-DR-β-A, -B, or -C to be used for HLA typing. (Strominger Decl. ¶¶ 33-34). Dr. Strominger views the Examiner's assertion is "scientifically unfounded". Indeed, the Examiner has not pointed to any scientific evidence to suggest that the full-length cDNA inserts of HLA-DR-β-A, -B, or -C could not be successfully used for HLA typing. In the absence of evidence to the contrary, the Examiner has no reason to doubt the objective truth of applicants' asserted operability of the present invention:

> "As a matter of Patent Office practice ... a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented, must be taken as in

> compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied upon for enabling support... [I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." Ex parte Kenaga, 189 USPQ 62, 64 (Pat. Off. Bd. Pat. App. 1975), quoting In re Marzocchi, 439 F.2d 220, 223-24, 169 USPQ 367, 369 (CCPA 1971) (emphasis in original).

For all of the foregoing reasons, the § 112, first paragraph rejection of claims 76-79 and 82-102 should be withdrawn.

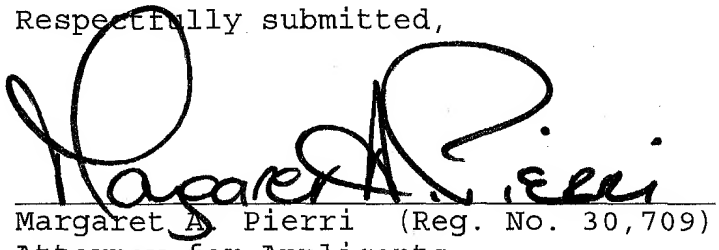
Obviousness-Type Double Patenting Rejection

The Examiner also maintained the rejection of claims 76 to 102 under the judicially created doctrine of obviousness-type double patenting as being "unpatentable" over claims 1 to 10 of United States Patent No. 5,503,976. Upon indication of allowable claims in this application, applicants stand ready to file a Terminal Disclaimer.

Applicants request that the Examiner consider the

foregoing amendments and remarks and pass this application to issue.

Respectfully submitted,



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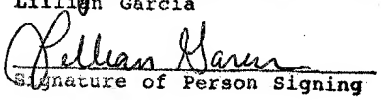

Signature of Person Signing

APPENDIX

78. (Amended) An HLA-DR typing process comprising the steps of:

(a) hybridizing DNA in a sample to be typed to a DNA sequence, said DNA sequence being capable of hybridizing to a polymorphic region of an HLA-DR-β chain locus of the human lymphocyte antigen complex to allow determination of one or more HLA-DR alleles, said polymorphic region being encoded by a DNA sequence selected from the group consisting of:

(i) DNA sequences encoding a majority of the amino acid sequence [in a region consisting essentially] of amino acids 8-14, 26-32 or 72-78 of a polypeptide sequence coded for by DNA insert DR-β-A, DR-β-B or DR-β-C;

(ii) DNA sequences which are allelic variants of any of the foregoing DNA sequences; and

(iii) DNA sequences which are fully complementary to any of the foregoing sequences, and

(b) detecting areas of hybridization between said DNA in said sample and said DNA sequence.

79. (Amended) An HLA-DR typing process comprising the steps of:

(a) restricting a first DNA isolated from an individual to be typed with at least one restriction endonuclease;

(b) size-fractionating said restricted DNA;

(c) hybridizing said size-fractionated DNA to be typed to a second DNA, said second DNA being capable of hybridizing to a polymorphic region of an HLA-DR-β chain locus of the human lymphocyte antigen complex to allow determination of one or more HLA-DR alleles, said polymorphic region being encoded by a DNA sequence selected from the group consisting of:

(i) DNA sequences encoding a majority of the amino acid sequence [in a region consisting essentially] of amino acids 8-14, 26-32 or 72-78 of a polypeptide sequence coded for by DNA insert DR-β-A, DR-β-B or DR-β-C;

(ii) DNA sequences which are allelic variants of any of the foregoing DNA sequences; and

(iii) DNA sequences which are fully complementary to any of the foregoing sequences, and

(d) detecting areas of hybridization between said size-fractionated DNA and said second DNA.